

## PD AND LOSS OF PERITONEAL FUNCTION

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**Abstract:** During long-term treatment with peritoneal dialysis both peritoneal membrane structure and function undergo significant changes that not only correlate with the time under treatment, but also with the frequency and severity of infections. In addition, peritoneal dialysis fluid bio-incompatibility may constitute a hazard for the longevity of the peritoneum as the dialysis membrane. In particular, the presence of glucose degradation products may lead to impaired peritoneal cell function as well as to increased protein glycation and peritoneal AGE deposition. Results from recent prospective randomised studies suggest that treatment with new GDP-depleted PD fluids may lead to a significant improvement of clinical outcomes in PD patients.

**Key words:** peritoneal dialysis, peritonitis, glucose degradation products.

### *Introduction*

The peritoneal membrane of patients undergoing long-term peritoneal dialysis is repeatedly exposed to an unphysiological environment that includes uraemic toxins, dialysis fluids, and plasticizers. In addition, many patients experience acute peritonitis episodes that are characterised by a massive leukocyte influx into the peritoneal cavity. This phenomenon is controlled by a complex network of cytokines and chemotactic factors. As a consequence of severe peritoneal inflammation a denudation of the peritoneal mesothelium and damage to

the underlying interstitium may follow. The ensuing wound-healing process involves the synthesis of extracellular matrix components and the repopulation of the denuded areas by mesothelial cells [1]. Recent *in vitro* studies suggest that this process may, however, be impaired in the presence of conventional PD fluids [2].

Peritoneal membrane changes may, however, also occur in patients who have never experienced a peritonitis episode. Typical morphological changes such as the thickening of the submesothelial compact zone are already present in pre-dialysis and haemodialysis patients; however, progressive membrane thickening and subendothelial hyalinization of blood vessels were reported to correlate with the duration of PD [3]. Likewise, the peritoneal membrane of animals with experimental uraemia shows higher vascularisation and permeability, with the accumulation of advanced glycation end-products (AGE) and angiogenic growth factors [4]. These alterations were further amplified by peritoneal dialysis.

Not only morphological, but also functional membrane alterations may depend on the type of dialysis solution that has been used. As an example, exposure of the peritoneal membrane to hypertonic glucose solutions was shown to correlate with an increase in solute transport over time [5]. In addition to glucose, glucose degradation products (GDP) may contribute to this phenomenon. In experimental animals, intra-peritoneal infusion of GDP-containing solutions results in a peritoneal accumulation of methylglyoxal, the GDP, and of AGE and their receptor (RAGE) [6]. AGE accumulation in the peritoneal membrane, on the other hand, correlates with changes in peritoneal transport and ultrafiltration [7, 8]. Exposure of peritoneal mesothelial cells to GDP increased the formation of AGE and expression of RAGE *in vitro* [9]. In turn, glycated proteins may activate the production of proinflammatory cytokines by mesothelial cells [10].

Moreover, during peritoneal dialysis mesothelial cells may undergo a transition from an epithelial phenotype to a mesenchymal phenotype, another process that may well be related to the mechanisms responsible for the development of high solute transport status [11, 12].

Overall, evidence to date suggests that in addition to the time under treatment and the frequency of infectious complications, the composition and biocompatibility of dialysis fluids are important determinants for the longevity and function of the peritoneal membrane. In earlier years, research on PD biocompatibility was focused on the acute effects of buffers, acidity, and hyperosmolality on peritoneal cell functions [13, 14]. More recently, however, evidence has accumulated that glucose degradation products are strongly involved in the pathogenesis of chronic peritoneal membrane dysfunction, either directly or indirectly via the enhanced formation and deposition of advanced AGE. As a consequence, PD fluids with neutral pH and reduced GDP content were developed and recently introduced into clinical practice. In these new glucose-based PD fluids highly concentrated glucose at a very low pH is separated from

catalyzing electrolytes and buffers in dual-chambered containers [15]. This not only allows the use of different buffer systems (bicarbonate; lactate; lactate/bicarbonate) but also facilitates a neutral or near-neutral pH after mixing of the two solution compartments prior to i.p. infusion.

In the meantime, a growing number of studies indicate that the in vitro biocompatibility profile of the new solutions is significantly improved compared to conventional PD fluids [16, 17]. In contrast, GDP exert direct cytotoxic effects on peritoneal mesothelial cells [18–20]. Animal experiments have indicated that, in contrast to conventional fluids, PD solutions with reduced GDPs content induce no major haemodynamic effects [21] and reduce the peritoneal deposition of AGE, RAGE and collagen [6]. Chronic exposure of rats to PD solutions with low GDP and neutral pH moreover resulted in less irritation to the peritoneal membrane and better preservation of mesothelial cell morphology, compared with animals receiving conventional solutions [22, 23].

Recent clinical trials and ex vivo-studies have added further evidence to the potential benefits of reducing GDP exposure. Patients treated with bicarbonate- and bicarbonate/lactate-buffered PD fluids displayed improved peritoneal macrophage function and host defence [24]. A randomized, prospective clinical trial compared a new 25 mmol/L bicarbonate plus 15 mmol/L lactate with a conventional 40 mmol/L lactate-buffered peritoneal dialysis solution and found relief of inflow pain and improved ultrafiltration in patients treated with the new solution [25]. Reduction of inflow pain was also reported in a randomized, double-blind, cross-over study of new bicarbonate (38 mM) or bicarbonate (25 mM)/lactate (15 mM) containing PD fluids [26]. Another two-year randomized clinical trial showed improved membrane transport characteristics and effluent CA-125, a proposed marker of peritoneal membrane integrity, with the new fluid as compared to standard PDF [27]. A highly significant increase in effluent CA-125 was also observed with Balance, a new lactate-buffered, dual-chambered solution, when compared to standard PD fluid in a large randomized prospective cross-over trial [28]. The increase in CA-125 following treatment with bicarbonate/lactate- or bicarbonate-buffered fluids was also confirmed by two prospective randomized trials in APD patients [29, 30]. Moreover, clinical studies using Balance [28], Gambrosol-Trio [31], and Bicavera (Schmitt CP *et al*, NDT 2003;18 Suppl 4: 210, abstract) reported a reduction of systemic AGE levels with the new solutions. These results suggest that the new solutions may have a clinical impact beyond the peritoneal membrane. In fact, the Euro Balance Trial [28] has already indicated that the use of the new PD solution was associated with an improvement in residual renal function. Finally, the data from a large Korean registry (more than 1.900 patients followed for more than 3 years) suggested the improved survival of patients treated with new PD fluid (Balance) compared to those receiving conventional PD fluid [32, 33]. Whilst

these results are very hopeful indeed they will need to be confirmed by randomised controlled trials.

### Conclusions

Chronic exposure of the peritoneum to conventional PD fluids induces alterations of both membrane structure and function that in some patients may ultimately result in ultrafiltration failure and inadequate dialysis. Whilst the precise mechanisms leading to this complication remain to be fully elucidated, evidence available to date suggests that the reduction of glucose degradation products by using new multi-chambered PD solutions may significantly attenuate this problem and potentially improve clinical outcomes in chronic PD patients.

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#### Резиме

### ПЕРИТОНЕАЛНА ДИЈАЛИЗА И ГУБИТОК НА ПЕРИТОНЕАЛНАТА ФУНКЦИЈА

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Во текот на долготрајниот третман со перитонеална дијализа двете, перитонеалната мембранска структура како и функцијата претрпуваат значајни про-

мени кои не само што корелираат со времето на третманот, но исто така и со фреквенцијата и јачината на инфекциите. Понатаму, и био-компатибилноста на перитонеалната дијализна течност може да претставува потенцијален ризик за долготрајноста на перитонеумот како дијализна мембрана. Посебно, присутноста на глукозните деградациски продукти можат да водат до влошена функција на перитонеалните клетки како и до покачени гликозилациски и перитонеални депозити на завршните продукти на гликозилацијата. Резултатите од скорешните проспективни рандомизирани студии сугерираат дека третманот со новите перитонеални течности со намалена концентрација на гликозилациски деградациски продукти може да даде значајно подобрување на клиничкиот исход кај пациентите на перитонеална дијализа.

**Клучни зборови:** перитонеална дијализа, перитонитис, гликоза деградациски продукти.

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